It is unclear from Daniels to what extent the preparation is actually pure since a single peak on ultracentrifugal analysis is not sufficiently sensitive to detect small amounts of impurities and, indeed, impurities that have the same or similar sedimentation constants could be present in fairly high amounts. Nevertheless, this is not the issue; it is recognized that bovine growth hormone had been sufficiently purified that its complete amino acid sequence could be determined and this sequence was published, for example, in Dayhoff, M.D. *et al.* Atlas of Protein Sequence and Structure (1978) 5:Suppl.3, pp. 345-352, as noted on page 1 of the application.

Briefly, applicants' position is that any bovine growth hormone prepared ultimately from bovine pituitaries is of such dubious purity with respect to the moieties that cause bovine spongiform encephalopathy (BSE) that it is essentially useless. The recombinantly produced bovine growth hormone of the invention, on the other hand, bears no risk of such contamination and thus can be used in bovine subjects without the inherent risks of the prior art pituitary-derived hormones. Applicants believe that this provides a clear patentable distinction over the compositions of the prior art. There appears to be agreement that the recombinant process for producing bovine growth hormone set forth in the application is inventive over the art; indeed, the parent application claiming this process has been allowed by the U.S. PTO. Applicants are certainly aware that preparation of a product by a patentable process does not confer patentability on the product unless the product itself is different from that that exists in the prior art. Applicants' position is that the product of the recombinant process *is* significantly different from the prior art preparations of bGH.

The recombinantly prepared bGH does not differ only by a "slight variation in purity or glycosylation" (indeed, bGH is not glycosylated in any event) and applicants certainly acknowledge the general desirability of a high degree of purity. The two products differ in that one can be used in cattle and the other cannot. One has a significant risk factor attached and the other does not.

Taking the points made by the Office in turn, the cited passage in the 1985 *Science* article which is said to indicate that the virus does not purify with growth hormone is clearly purely speculative. The Office has failed to read the very next sentence after the indicated passage which states

> "This is very encouraging but we don't feel it is conclusive," says Judith Fradkin, Head of the Endocrinology Branch at the Arthritis Institute.
>
> Even if a repeat of the British test produces similar results, there is some uncertainty about extrapolating the findings to Creutzfeldt-Jakob virus.

In addition, there is considerable confusion about whether a virus is being dealt with at all. In the later article in *Science*, also included with the previous response, *Science* (1991) 252:1515-1522, Stanley Prusiner describes BSE and Creutzfeldt-Jakob disease (CJD) as well as kuru as caused by prions rather than viruses. There is still evidently some controversy over the causative agent; nevertheless, there is now considerable evidence that all of these diseases, including scrapie, are caused not by viruses but by prions, which are themselves proteins. See the attached article in *BioWorld Today* (1996) 7:No.247. See in particular page 4, left-hand column for a summary of the nature of prions and the right-hand column with respect to questions raised concerning its role as the sole causative agent. See also: *Science News* (1996) 150:282. Taken in these contexts, the quotation cited by the Office in the *Science* article is nonprobative at best since apparently viruses were sought and prions may be the culprits. Furthermore, as stated above, a single peak in ultracentrifugation is not probative of homogeneity. For example, the level of sensitivity of ultracentrifugation is much lower as compared to later-devised techniques such as HPLC. Considering the elusive nature of the disease-causing moiety, one of ordinary skill would not find it credible that assurances could be made that no disease-causing agents were present in this preparation.

Having said the foregoing, applicants agree that it is unlikely that the particular sample prepared by Daniels or any particular prior art preparation of purified bGH contained the disease-

causative agent for BSE or CJD. What characterizes the samples is the risk that these causative agents may, indeed, be contaminants as is further explained below.

Applicants respectfully submit that it is not sufficient that it be "very unlikely" that bovine growth hormone prepared from pituitaries contains the BSE-causing agent. It is very unlikely that any individual piece of beef sold in Britain over the last few years contained this agent. Undoubtedly, there were millions of beef cuts sold that did not contain it. However, the small likelihood that some of the beef sold contained this agent was sufficient to justify slaughtering over a million cattle. (See *BioWorld Today* (*supra*) page 1.)

The second point raised by the Office is that Daniels' preparation was presumably made from American cows, and therefore unlikely to contain the BSE disease-causing agent. Of course, Daniels is silent as to where the "art-known bovine growth hormones" were obtained (column 1, lines 40-43). Nevertheless, applicants are willing to concede the point that it is unlikely that the particular preparation prepared by Daniels contained this agent. As is clear from the enclosed *BioWorld Today* article as well as the clipping from the *The Washington Post* of January 3, 1997, both CJD and BSE are extremely rare. Therefore, any specific preparation of bGH of the prior art might be, and indeed is likely to be, free of this causative agent. The point is that it cannot be guaranteed to be thus free, and therefore it cannot be used. The enclosed *Post* article should be persuasive of the necessity for such guarantees in order for such products to be used. Despite an estimated cost of $21-48 million per year, the FDA proposes to prohibit the use of animal parts in cattle feed. The reason? The very *unlikely* possibility that some of this feed will be contaminated with the disease-causing agent.

The third point raised by the Office is that advantages not disclosed in the application cannot be urged as a basis for allowance. This, applicants respectfully submit, is not an accurate statement of the law. See, for example, *In re Chu*, 36 U.S.P.Q.2d 1089 (Fed. Cir. 1995). The Office modifies its statement to provide an exception where the advantage would inherently flow from what was originally disclosed in the specification.

The advantage does, indeed, inherently flow from the original disclosure. Recombinantly produced bGH is inherently free of the disease-causing agents of BSE and CJD. The freedom of the invention bGH from any risk of containing the disease-causing agents is directly relevant to the stated use of bGH in the application -- to stimulate the growth of cattle.

The fact that the advantage might not have been known at the time the application was filed is completely irrelevant. If the Office has any case law to support its position that later-found knowledge of the inherent advantages is irrelevant to their use as a basis for patentability, applicants would appreciate it being called to their attention so that they can properly respond.

The case law cited by the Office, *In re Davies*, 177 U.S.P.Q. 381, 385 (C.C.P.A. 1973) and *In re Zenitz*, 142 U.S.P.Q. 158 (C.C.P.A. 1964) does not support the Office's position. In *Davies*, the claims at issue were directed to copolymers containing butadiene whereas prior art disclosed homopolymers thereof. Applicants relied on the advantage that the products had "improved gloss, transparency and processability." The court found that these properties did not inherently flow from the disclosure because they were inconsistent with statements made in the specification that such properties would not be found when improvements in mechanical properties were obtained, and the specification focused on mechanical properties. Further, the specification made no distinction between homopolymers and copolymers, the applicants apparently not being aware that the homopolymers were prior art. The decision related to whether affidavits as to these properties should be considered in the face of these contradictions. The *Davies* court had a different solution. It stated that because the application in *Davies* met the requirements of 35 U.S.C. § 112, and "there is no specific statutory requirement that compels an applicant to disclose all properties of chemical compounds or compositions in his application," the applicant could remedy the lack of disclosure by filing a continuation-in-part providing a statement of these properties which would be entitled to the priority date of the original application. This is hardly consistent with the view that later-discovered inherent properties cannot be used to support patentability.

The *Zenitz* case is fully supportive of applicants' position. The claims in *Zenitz* were directed to compounds that were disclosed as useful as tranquilizers as well as hypotensives, sedatives, etc. The court stated

> It is true he made no mention of the separation of hypotensive and tranquilizing activity, but as with the celluloid top in *Westmoreland*, the advantage of minimized hypotensive activity would inherently flow from the indicated use of the compounds as tranquilizers.

Similarly, here, the present application discloses that bovine growth hormone may be administered to young cattle in order to increase their rate of growth and weight gain, thereby decreasing the time required between birth and marketing for beef. (See pages 1-2, bridging paragraphs.) The inherent advantage of having zero risk of transmitting BSE would inherently flow from this use, just as would low hypotensive activity inherently flow from the use of Zenitz's compounds as tranquilizers.

The *Zenitz* court distinguished the earlier holding in *In re Herr*, 134 U.S.P.Q. 176 (C.C.P.A. 19__) where an affidavit presented evidence of oral anabolic and andrenergic activity of certain claimed compounds. In that case, the specification mentioned as the sole utility of these compounds their use as intermediates in making other compounds. Thus, the inherent properties would not flow from the use disclosed.

The *Herr* situation is, of course, not the case here.

Finally, applicants, as stated above, agree that it is the product of the disclosed process that must be distinguished from the art; the process *per se* will not confer patentability if the product itself is not patentable. The Office states that when a prior art product reasonably appears to be the same as that claimed but differs only by the process by which it was produced, the burden is upon applicants to prove a patentable difference by comparative evidence. Whether comparative evidence is the only manner in which such differences can be shown is not clear, but this is a moot point since in the present case, the prior art product does not appear to be the same as that claimed. The evidence of record clearly shows that the product obtained is, in fact,

different. It is quite evident, given the evidence of record, that there would be no possibility of administering the prior art product to any cattle, as described in the specification, to enhance their growth rate. The recombinant product, on the other hand, as was the case with human growth hormone, would be considered not to carry the risks carried by the prior art product.

Respectfully, it is believed that the Office is taking too literal a view of what constitutes the characteristics or properties of a composition. It is applicants' position that the risks attached to the use of a product are as much a property of this product as any physical characteristics thereof.

Conclusion

In view of the foregoing, applicants believe that the pending claims 19-22 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: January 16, 1997

Respectfully submitted,

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